More Intensive Dialysis Does Not Improve Outcomes among Patients with Acute Kidney Injury

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Acute kidney injury (also called "acute renal failure") is a serious medical condition characterized by a relatively rapid loss of kidney function, usually over a period of several hours or days. The resulting inability to excrete nitrogenous waste products and maintain fluid and electrolyte balance poses urgent health problems for patients and their physicians. Acute kidney injury may arise from a number of causes, most commonly sepsis (a serious, whole-body inflammatory reaction caused by infection), decreased blood pressure, or kidney damage from drugs or other toxins. It is a relatively common complication among hospitalized patients; it affects between 2 and 7 percent of all hospitalized patients.[1] Even though a significant fraction of patients with acute kidney injury will regain kidney function, many do not, and this medical condition is associated with high in-hospital mortality rates ranging from 50 to 80 percent among the critically ill.[1]

There is no effective drug therapy to reverse acute kidney injury. The goal of treatment is to prevent fluid and waste from building up in the body while waiting for the kidneys to resume functioning. Treatment involves hemodialysis and other forms of life-sustaining therapy to replace lost kidney function. Dialysis removes waste products from the blood, and it also helps control blood pressure and keeps the proper electrolyte balance.

Although dialysis has been used to treat acute kidney injury for over 60 years, it is still not clear when it is best to initiate therapy, which method of dialysis is best to use, and what dose of dialysis to deliver. Several recent, small studies had suggested that increased frequency or intensity of dialysis might improve survival in patients with acute kidney injury. However, the results of these studies have not been definitive. This uncertainty raises the possibility that some patients may be receiving a sub-optimal dose or frequency of dialysis, or that other patients may be receiving excessive dialysis that may carry no clinical benefit and may, in fact, expose them to unnecessary risk. In order to investigate this issue, the NIDDK partnered with the U.S. Department of Veterans Affairs to launch a clinical trial comparing "standard" with "intensive" dialysis in patients with acute kidney injury.

Design of the ATN Study

The VA/NIH Acute Renal Failure Trial Network (ATN) Study was designed to determine whether higher-dose (intensive) dialysis would reduce the death rate, shorten the duration of the illness, and decrease the number of complications in other organs among patients with acute kidney injury, as compared to standard-dose dialysis. It enrolled over 1,100 critically

ill patients—defined as patients with acute kidney injury as well as either sepsis or the failure of at least one other organ. Notably, the trial did not enroll patients with chronic kidney disease. These patients were not studied in this trial because the causes and progression of their acute kidney injury are different from that seen in people without underlying chronic kidney disease.

Patients were randomly assigned to receive intensive- or standard-dose dialysis. Patients who did not require medications to maintain their blood pressure were treated with conventional dialysis, either three times per week in the standard arm of the study or six times per week in the intensive arm. Patients with very low blood pressure who required medications to increase their blood pressure were treated with more gentle forms of dialysis, either a slower form of hemodialysis, three or six times per week, or a continuous form of dialysis, at a lower or higher dose, as randomly assigned. One important element in the design of the study was that patients were able to switch between forms of therapy as their clinical condition changed, while remaining within the lower or higher intensity treatment arms of the study. This approach reflects typical clinical practice in that it allowed physicians to adjust the method of dialysis as the patient's condition changed, and was chosen so that the results of the trial would be more relevant to actual patient care.

Results of the ATN Study: Is More Better?

The primary question the trial was designed to answer was whether more intensive dialysis provided a clinical benefit. The first, and perhaps most important, clinical endpoint was patient survival. After 60 days, no significant difference in rates of death by any cause was found between the two groups of patients. Over this period, 289 of 561 patients (51.5 percent) in the standard-dose treatment group died, compared to 302 of 563 patients (53.6 percent) in the intensive treatment group. Mortality rates were similar in men and women and across racial and ethnic subgroups.

When the researchers assessed kidney function and other medical conditions, similar patterns were seen. A total of 102 patients (18.4 percent) in the standard-dose group had complete recovery of kidney function after 28 days, and 50 patients (9.0 percent) had partial recovery. By comparison, 85 patients (15.4 percent) in the intensive-treatment group had complete recovery of kidney function over the same time period, and 49 patients (8.9 percent) had partial recovery. A total of 92 patients (16.4 percent) undergoing less-intensive therapy were able to return home without requiring continued dialysis after 60 days, compared to 88 patients (15.7 percent) who underwent intensive therapy. None of these differences between groups was statistically significant. Rates of treatment-related complications across all groups were also similar.

In summary, the ATN Study found no significant differences between the two groups in recovery of kidney function, the rate of failure of organs other than kidneys, or the number of patients able to return home after recovery. In patients enrolled in this trial, there was no benefit to intensive dialysis.

Implications of the ATN Study

Although a few studies have suggested that increased frequency or intensity of hemodialysis might improve survival in patients with acute kidney injury, they have been small and conducted at single sites. In contrast, the ATN study enrolled over 1,100 patients from 17 Veterans Affairs medical centers and 10 university-affiliated medical centers across the U.S. The results of the larger ATN Study show that when it comes to dialysis in acute kidney injury, more is not better.

The results of the ATN study, however, should be interpreted carefully. One limitation of the ATN study concerns the exclusion from the trial of patients with advanced chronic kidney disease. Such patients make up a substantial proportion of people who develop acute kidney injury. Therefore, it may be inappropriate to extrapolate the ATN results to persons in whom acute kidney injury develops in

the context of pre-existing chronic kidney disease. Further study will be necessary to resolve this longstanding question and address the optimal treatment of acute kidney injury in this population.

Conclusion

The results of the ATN study indicate that increasing dialysis treatments to five to six times per week does not confer an additional benefit beyond a standard three times per week regimen. However, this does not mean that dose of dialysis does not matter. The dose of dialysis targeted in the standard-treatment group was greater than what is often achieved in a typical clinical setting. The results also do not mean that higher doses of continuous therapies are never beneficial, only that routine use of higher-dose dialysis is unnecessary. Nevertheless, the findings of this study may spare patients from unnecessarily-intensive medical interventions. They also underscore the importance of continued research into other approaches to treating acute kidney injury. Future research efforts may include studies to identify biomarkers of kidney injury prior to renal failure, which could enable physicians to predict who is likely to develop acute kidney injury, to lessen its severity through earlier intervention, or to preempt this life-threatening condition altogether.

The NIDDK has begun a new initiative entitled "Identification and Evaluation of Biomarkers and Risk Assessment Tools for Chronic Kidney Disease and Acute Kidney Injury." The goal of this initiative is to identify and validate biomarkers and risk assessment tools for kidney function, injury, and progression. Both existing and new biomarkers and risk assessment tools will be rigorously evaluated for clinical utility under this initiative. In addition to seeking new molecular markers in chronic kidney disease and acute kidney injury, the initiative will also examine whether these two conditions share common biomarkers.

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[1] *Palevsky PM, et al: Intensity of renal support in critically ill patients with acute kidney injury. NEJM 359:7-20, 2008.*